



Neurological Complications of Pulmonary Embolism: a Literature Review

Parth V. Desai¹ · Nicolas Krepostman² · Matthew Collins² · Sovik De Sirkar² · Alexa Hinkleman² · Kevin Walsh² · Jawed Fareed³ · Amir Darki¹

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Abstract

Purpose of Review The present review discusses in-depth about neurological complications following acute venous thromboembolism (VTE).

Recent Findings Intracranial hemorrhage, acute ischemic cerebrovascular events, and VTE in brain tumors are described as central nervous system (CNS) complications of PE, while peripheral neuropathy and neuropathic pain are reported as peripheral nervous system (PNS) sequelae of PE. Syncope and seizure are illustrated as atypical neurological presentations of PE.

Summary Mounting evidence suggests higher risk of venous thromboembolism (VTE) in patients with neurological diseases, but data on reverse, i.e., neurological sequelae following VTE, is underexplored. The present review is an attempt to explore some of the latter issues categorized into CNS, PNS, and atypical complications following VTE.

Keywords Pulmonary embolism · Venous thromboembolism · Neurological complications · Cerebrovascular disease

Abbreviations

ACCP	American College of Chest Physicians
ASA	Atrial septal aneurysm
ASD	Atrial septal defect
CDT	Catheter-directed thrombolysis
CNS	Central nervous system
CS	Cryptogenic stroke
CTEPH	Chronic thromboembolic pulmonary hypertension
DIC	Disseminated intravascular coagulation
DOAC	Direct-oral anticoagulant
DVT	Deep vein thrombosis

ESUS	Embolic stroke of uncertain etiology
ICH	Intracranial hemorrhage
IVC	Inferior vena cava
LMWH	Low molecular weight heparin
MI	Myocardial infarction
MTS	May-Thurner syndrome
ORBI	Outpatient bleeding risk index
PE	Pulmonary embolism
PESI	Pulmonary Embolism Severity Index
PFO	Patent foramen ovale
PNS	Peripheral nervous system
PTS	Post-thrombotic syndrome
RLS	Right-to-left shunt
SARS	Severe acute respiratory syndrome
SUCRA	Surface under the cumulative ranking curve
TS	Trousseau syndrome
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

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✉ Amir Darki
amirdarki@gmail.com; ADARKI@lumc.edu

¹ Department of Cardiovascular Medicine, Loyola University Medical Center, Maywood, IL 60153, USA

² Department of Internal Medicine, Loyola University Medical Center, Maywood, IL 60153, USA

³ Department of Pathology and Laboratory Medicine and Department of Pharmacology and Neuroscience, Health Science Division, Cardiovascular Research Institute, Hemostasis and Thrombosis Research Division, Loyola University, Maywood, IL 60153, USA

Introduction

Venous thromboembolism (VTE), a term collectively referred for deep vein thrombosis (DVT) and pulmonary embolism (PE) is often underdiagnosed and potentially life threatening. This preventable medical condition is the

third most common cause of cardiovascular mortality [1], with an estimated incidence of 1–2 cases per 1000 persons (~900,000 cases) per year in the USA [2]. According to a 2016 study, annual incident VTE is estimated to cost the US healthcare system about \$7–12 billion (2014 US dollars) annually [3]. Venous stasis, hypercoagulability, and endothelial injury (commonly known as Virchow's triad) are key factors underlying VTE pathophysiology [4]. Numerous acquired and inherited risk factors (advancing age, obesity, recent surgery or hospitalization, active cancer, trauma or fracture, immobility or paralysis, pregnancy or puerperium in women, oral contraceptives or hormonal therapy, and several inherited thrombophilia) predispose individuals to thrombosis [2].

VTE as a sequela of neurologic disease is widely established. Various neurological disorders contribute to immobility and hypercoagulability. The incidence of VTE within the first 3 months after acute ischemic stroke is 15% compared to 0.2% in the general population [5]. Compared to the thrombotic consequences of neurologic disease, the neurologic complications of VTE are less studied. In this review article, we sought to discuss the neurological sequela of VTE.

Classification, Severity, and Complications of Venous Thromboembolism

DVTs are classified based on location and etiology. Lower limb DVT with thrombi proximal to the popliteal trifurcation is labeled as proximal whereas below is identified as distal DVT. Upper limb DVT is far less common than lower extremity but still account for 10% of DVTs, predominantly related to indwelling central venous catheters and cardiac leads from pacemakers and defibrillators [6]. The etiology of DVT as provoked (with underlying trigger)

versus unprovoked (without an identifiable trigger) and temporary (reversible trigger) versus permanent (irreversible trigger) [7] helps guide duration of treatment and risk of recurrence. [8]. Although majority of distal DVT spontaneously resolve with minimal symptoms, significant morbidity can be caused by thrombi extending into popliteal, femoral, and other proximal veins [9, 10].

Common complications of DVT include post-thrombotic syndrome (PTS), PE, and sudden death [11]. If left untreated, there is a 50% chance that proximal DVT will cause symptomatic PE within 3 months [10, 12]. PTS occurs in about 30–50% DVT patients which sometimes result in lifelong limb pain, swelling, heaviness, edema, telangiectasias, lipodermatosclerosis, and leg ulcers [13–15]. In patients with proximal DVTs, 30–40% are likely to develop PE, while 70% of patients with PEs have concomitant DVT [16]. Estimate suggests that 10–30% people die of VTE within 1 month of diagnosis with about a quarter of people presenting as sudden death [2]. Data also suggests about one third (33%) of the patients with VTE would have recurrence within 10 years of initial diagnosis [2].

Acute PE is classified per the American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines into massive, sub-massive (high/intermediate risk), and low risk (Table 1) based on the hemodynamic stability and end-organ damage (elevated cardiac biomarkers and right ventricular strain) [17, 18]. This classification helps to stratify risk of decompensation and guides in management decisions [17–19]. Pulmonary Embolism Severity Index (PESI) and simplified PESI (sPESI) are incorporated into the ESC guidelines for further risk stratification [20, 21].

While acute massive PE can cause immediate cardiorespiratory failure resulting in death, longstanding PE can cause chronic thromboembolic pulmonary hypertension

Table 1 Criteria for risk- stratification of acute pulmonary embolism

	Risk Profile	Shock or Hypotension	RV Dysfunction	Cardiac Biomarkers	PESI Class III-V or sPESI ≥ 1
ESC	High	+	+	+	+
	Intermediate-High	-	+	+	+
	Intermediate-Low	-	Either one (or none) positive		+
	Low	-	-	-	-
AHA	Massive	+			
	Submassive	-	Either one positive		
	Low	-	-	-	

Abbreviations: ESC – European Society of Cardiology, AHA – American Heart Association

(CTEPH) and eventually right heart failure [22]. Given that all forms of VTE will need some form of anticoagulation, hemorrhagic complications in the forms of gastrointestinal, central nervous system (CNS), genitourinary, pulmonary, and other vascular bleeding are not uncommon [9]. Between 2 and 5% of patients with VTE could experience major bleeding within 3 months [23].

Neurological Complications of Venous Thromboembolism

Neurological complications following VTE can be divided into three groups (Fig. 1):

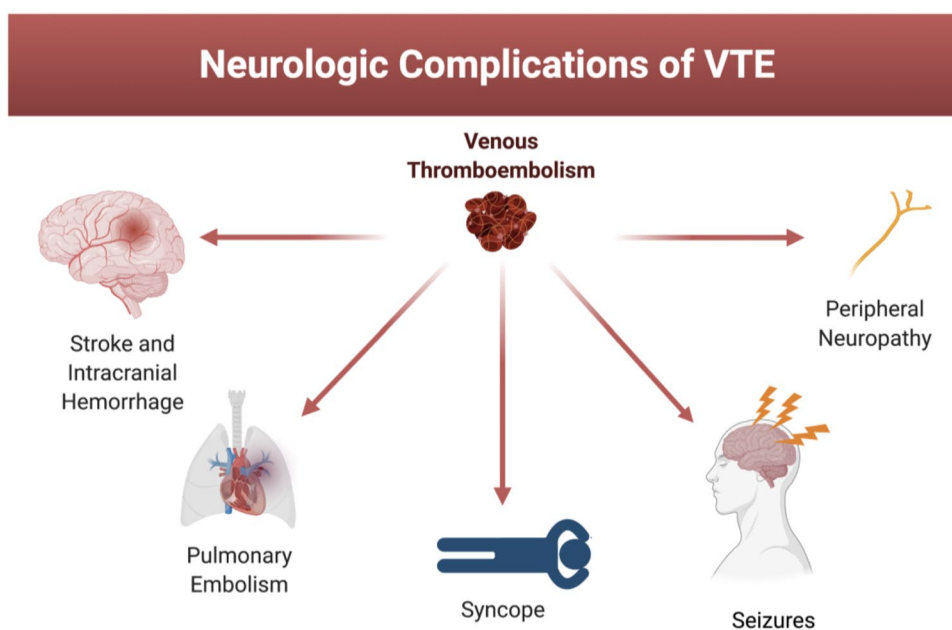
- (i) CNS complications:
 - Intracranial hemorrhage
 - Ischemic stroke
 - VTE in CNS tumor
- (ii) Atypical presentations of PE
 - Syncope
 - Seizure
- (iii) Peripheral nervous system (PNS) complications
 - Peripheral neuropathy
 - Neuropathic pain syndromes.

Intracranial Hemorrhage

Intracranial hemorrhage (ICH) is the most feared and well-described complication of VTE linked to the treatment of VTE. Standard therapy for VTE involves the use of anticoagulation and/or thrombolytics depending on severity of presentation and with varying risk of ICH. Intracranial hemorrhage is attributed to significant morbidity and mortality [24], as less than half of patients with ICH survive at 1 year and less than one third survive at 5 years [25]. True incidence is difficult to determine and varies according to anticoagulant or thrombolytic used [26]. Risk factors for overall bleeding include older age, female sex, prior bleeding, peptic ulcer disease, active cancer, hypertension, prior stroke, renal or liver disease, and alcohol abuse [27].

Treatment decisions in VTE involve weighing risks and benefits. Most patients with VTE can be treated as outpatients with direct-oral anticoagulants (DOACs), vitamin K antagonists (VKAs), or low molecular weight heparin (LMWH) [16]. For proximal leg DVTs or PE in the absence of cancer, the American College of Chest Physicians (ACCP) recommends treatment with DOAC such as dabigatran, rivaroxaban, apixaban, or edoxaban over VKA, such as warfarin [18]. DOACs have been shown to prevent recurrence of symptoms and early death in PE [28]. In clinical practice, they have been readily used for their convenience in dosing and administration and reduced overall bleeding risk [29]. A meta-analysis of 17 RCTs by Wolfe et al. examined comparative risk of ICH between different DOACs and reported risk of ICH as odds ratio compared to control (aspirin, warfarin, and LMWH) [30•]. Reported rates of ICH

Fig. 1 Central illustration showing neurologic complications of VTE



with each anticoagulant from prospective trials are listed in Table 2. Patients with absolute contraindications or failure with anticoagulation may be considered for inferior vena cava (IVC) filter placement, although studies have not shown reduced mortality [31].

The use of thrombolytics is reserved for patients with massive PE and selected cases of sub massive PE with higher risk for clinical deterioration. Current ACCP guidelines recommend thrombolytics in patients with acute PE and associated hypotension without high bleeding risk (grade 2B) [18].

Streptokinase, urokinase, and alteplase are currently the only FDA-approved thrombolytics for PE [32]. These agents work by activating plasminogen, causing clot lysis and ultimately improving pulmonary artery pressure and pulmonary

perfusion [32]. Thrombolytic therapy has been shown to improve mortality in high-risk population and prevent the development of CTEPH [33–36]. However, improvement in these outcomes comes at the cost of increased risk of ICH (Table 3), with a reported incidence rate of 1–3% depending on agent used [55]. Absolute contraindications for thrombolytics include structural intracranial disease, previous ICH, ischemic stroke within 3 months, active bleeding, recent brain or spinal surgery, recent head trauma or brain injury, or bleeding diathesis [18]. A meta-analysis of 26 trials including 2784 patients by Izcovich et al. showed an increase in ICH (RR 3.17, 95% CI 1.19–8.41) with the use of thrombolytics compared to controls [56]. The largest trial evaluating the use of full dose systemic tPA for acute submassive

Table 2 Anticoagulants used for VTE in various studies

<i>Drug and dose</i>	<i>Indication/mechanism</i>	<i>Rate of ICH</i>	<i>Study, Year</i>
Apixaban 2.5 mg	VTE prophylaxis/Xa inhibitor	0/3184 (0%)	ADOPT, 2011
		0/1595 (0%)	ADVANCE, 2009
Apixaban 2.5 mg	AF/Xa inhibitor	0/72 (0%)	ARISTOTLE, 2011
Apixaban 5 mg	AF/Xa inhibitor	0/71 (0%)	ARISTOTLE, 2011
		11/2808 (0.39%)	AVERROES, 2011
		3/2676 (0.11%)	AMPLIFY, 2013
Dabigatran 110 mg	AF/thrombin inhibitor	27/6015 (0.44%)	RE-LY, 2009
Dabigatran 150 mg	AF/thrombin inhibitor	36/6076 (0.59%)	RE-LY, 2009
Dabigatran 150 mg	VTE/thrombin inhibitor	0/1274 (0%)	RE-COVER I, 2009
		2/1270 (0.16%)	RE-COVER II, 2014
		2/1430 (0.14%)	RE-MEDY, 2013
Edoxaban 60 mg	VTE/Xa inhibitor	5/4118 (0.12%)	Hokusai-VTE, 2013
		2/522 (0.38%)	Hokusai-VTE Cancer, 2017
Edoxaban 60 mg	AF/Xa inhibitor	61/7012 (0.87%)	ENGAGE AF-TIMI 48, 2013
Rivaroxaban 10 mg	VTE prophylaxis/Xa inhibitor	2/3997 (0.05%)	MAGELLAN, 2013
Rivaroxaban 15 mg	AF/Xa inhibitor	63/637 (9.89%)	J ROCKET-AF, 2012
Rivaroxaban 20 mg	AF/Xa inhibitor	55/7111 (0.77%)	ROCKET-AF, 2011
Rivaroxaban 20 mg	VTE/Xa inhibitor	1/2412 (0.04%)	EINSTEIN-PE, 2012
LMWH	VTE prophylaxis/antithrombin activator	1/1588 (0.06%)	ADVANCE, 2009
		2/3217 (0.06%)	ADOPT, 2011
		0/4001 (0%)	MAGELLAN, 2013
LMWH	VTE/antithrombin activator	4/524 (0.76%)	Hokusai-VTE Cancer, 2017
Warfarin	VTE/vitamin K antagonist	6/2689 (0.22%)	AMPLIFY, 2013
		10/2405 (0.42%)	EINSTEIN-PE, 2012
		18/4122 (0.44%)	Hokusai-VTE, 2012
		3/1265 (0.24%)	RE-COVER I, 2009
		6/1289 (0.47%)	RE-COVER II, 2014
		4/1426 (0.28%)	RE-MEDY, 2013
Warfarin	AF/vitamin K antagonist	122/9052 (1.34%)	ARISTOTLE, 2011
		13/2791 (0.47%)	AVERROES, 2011
		132/7012 (1.88%)	ENGAGE AF-TIMI 48, 2013
		87/6022 (1.44%)	RE-LY, 2009
		84/7126 (1.1%)	ROCKET-AF, 2011
		76/637 (11.9%)	J ROCKET-AF, 2012

Table 3 Thrombolytics and their doses used in various studies

<i>Drug and dose</i>	<i>Indication/mechanism</i>	<i>Rate of ICH</i>	<i>Study, Year</i>
t-PA 0.6 mg/kg	Thrombolysis/plasminogen activator	0/33 (0%) 0/60 (0%) 0/36 (0%)	Levine et al., 1990 [37] Goldhaber et al., 1994 [38] Sors et al., 1994 [39]
t-PA 10–20 mg	Thrombolysis/plasminogen activator	0/30 (0%)	Kucher et al., 2014 [40]
t-PA 40–80 mg	Thrombolysis/plasminogen activator	0/9 (0%)	PIOPED, 1990 [41]
t-PA 50 mg	Thrombolysis/plasminogen activator	1/55 (1.81%) 0/61 (0%)	Wang et al., 2010 [42] Sharifi et al., 2013 [43]
t-PA 100 mg	Thrombolysis/plasminogen activator	0/13 (0%) 2/44 (4.54%) 2/27 (7.41%) 0/34 (0%) 0/17 (0%) 0/118 (0%) 0/7 (0%) 0/48 (0%) 0/37 (0%)	Tebbe et al., 1999 [44] Goldhaber et al., 1993 [45] Goldhaber et al., 1994 [38] Meyer et al., 1992 [46] Sors et al., 1994 [39] Konstantides et al., 2002 [47] Muhl et al., 2007 [48] Wang et al., 2010 [42] Fasullo et al., 2011 [49]
r-PA 20 units	Thrombolysis/plasminogen activator	0/23 (0%)	Tebbe et al., 1999 [44]
STK 2.65–5.05 million units	Thrombolysis/plasminogen activator	1/75 (1.33%)	Patra et al., 2014 [50]
STK 9 million units	Thrombolysis/plasminogen activator	0/8 (0%)	Muhl et al., 2007 [48]
Urokinase 57,200 units/kg	Thrombolysis/plasminogen activator	1/29 (3.44%)	Meyer et al., 1992 [46]
Urokinase 3 million units	Thrombolysis/plasminogen activator	1/45 (2.22%)	Goldhaber et al., 1992 [51]
TNK 30–50 mg	Thrombolysis/plasminogen activator	1/28 (3.55%) 0/25 (0%) 10/506 (1.98%) 1/40 (2.5%)	Becattini et al., 2010 [52] Patra et al., 2014 [50] Meyer et al., 2014 [53] Kline et al., 2014 [54]

PE was the PEITHO trial—a multicenter, double-blinded study randomizing 1005 patients with submassive PE to either placebo vs weight-based tenecteplase [57]. The trial demonstrated a significant reduction in the primary endpoint of death and hemodynamic collapse (2.6%). However, the fibrinolytic treatment was associated with an unacceptable 2.0% rate of hemorrhage stroke and 6.3% rate of major extra cranial hemorrhage.

As bleeding complications from thrombolytics are thought to be dose-dependent, various studies investigating optimal dosing have suggested lower doses are equally efficacious with less bleeding risk [58]. Reduced dose thrombolytics are potentially beneficial in high-risk populations such as elderly, pregnant, surgical candidates, and patients weighing less than 65 kg [59]. A meta-analysis of five trials consisting of 440 patients conducted by Zhang et al. compared low dose rt-PA (50 mg over 2 hours) to standard dose

(100 mg over 2 hours) which showed no statistical difference in recurrent PE or all case mortality with few major bleeding events [32, 60]. Additionally, the MOPPET trial randomized 121 patients with submassive PE to either low dose alteplase (0.5 mg/kg, max 50 mg) or anticoagulation alone and found a reduced incidence of pulmonary hypertension and recurrent PE in the thrombolytic group with no bleeding events reported in either group [43].

In addition to low-dose thrombolytics, catheter-directed thrombolysis (CDT) has also been studied to reduce hemorrhagic risk in patients with acute PE. The goal of CDT is to locally deliver thrombolytics to the site of thrombus with reduced bleeding risk compared to systemic thrombolytics [61]. The ideal candidate is stable enough to tolerate a prolonged infusion and has a proximal thrombus [40, 62, 63•]. Three prospective trials ULTIMA, SEATTLE II, and PERFECT have shown that CDT can be efficacious with

relatively low bleeding risk [63•]. The ULTIMA trial randomized 59 patients to CDT plus heparin vs heparin alone and found improvement in RV/LV ratio with no major bleeding in the CDT group [40]. SEATTLE II was a prospective single-arm trial that included 150 patients treated with CDT and found statistical improvement in hemodynamic parameters, with 17 major bleeds but no ICH [62]. The PERFECT registry examined 101 patients with catheter-directed mechanical thrombectomy and/or CDT, with main outcome being composite of hemodynamic parameters and survival to hospital discharge [64]. Their results showed improvement in these measures without major bleeding events, including ICH [64]. While these studies have limitations, they provide evidence that CDT can be safe and efficacious treatment option for acute PE in appropriate patients [63•].

Given the complexity in selecting therapy for VTE patients, multiple bleeding stratification scores have been developed. Scores such as REITE score, outpatient bleeding risk index (OBRI), the Dutch score, and Kuijer scores have all been trialed [65]. The HAS-BLED score, a bleeding stratification tool used for anticoagulation in atrial fibrillation, has also recently been studied in the VTE population and found to have predictive validity. A large retrospective study of 132,280 VTE patients found that patients with scores greater than four were at higher risk for bleeding events [66].

Ischemic Stroke Following VTE

Compared to hemorrhagic stroke, less is known about subsequent arterial events such as ischemic stroke following VTE. One of the earliest known associations between VTE and atherosclerotic disease is that patients with unprovoked DVTs are more likely to have asymptomatic carotid disease [67]. While the mechanism for this association remains unclear, some contribution is likely due to shared risk factors including obesity, diabetes, and dyslipidemia [68, 69]. Srenson et al. assessed myocardial infarction (MI) and stroke risk in patients with DVT/PE and found the relative risk of ischemic stroke in the first year for PE patients was 2.93 (95% CI 2.34–3.66) and 2.19 (95% CI 1.85–2.6) for DVT patients, with similar risk with either provoked or unprovoked disease [68]. A 2010 meta-analysis by Becattini et al. that included 17 studies found an increased risk of arterial cardiovascular diseases in patients with unprovoked VTE compared to provoked VTE [52]. Madidrano et al. examined the REITE registry composed of 12,397 PE patients and 10,973 DVT patients for development of subsequent ischemic events while on anticoagulation and found 45 patients with PE suffered ischemic stroke compared to 41 patients with DVT, with subsequent death in 13 and 6 patients, respectively [70].

Patent Foramen Ovale, VTE, and Risk of Stroke

Patent foramen ovale (PFO) is a persistent fetal communication between the right and left atria due to failure of primum and secundum atrial septa to fuse postpartum. Although the prevalence of PFO is ~25% in the general population, the prevalence increases to nearly 50% in young patients (<55 years) who present with cryptogenic ischemic stroke [71•]. Under certain hemodynamic conditions with right-to-left atrial shunt (RLS) (e.g., PFO, atrial septal defect (ASD) or atrial septal aneurysm (ASA)) blood and bloodborne products migrate from venous circulation to arterial system leading to paradoxical embolism as reported previously [72–74].

Concomitant PE and acute ischemic stroke is a rare event but has been described in various case reports and series [75–78, 79••, 80, 81, 82•, 83]. Treatment of simultaneous PE and acute stroke is challenging due to competing benefits of systemic thrombolytics with risk of hemorrhagic conversion of acute stroke [80, 81]. Lio et al. reviewed 29 concomitant high-risk PE and acute stroke patients (with 90% prevalence of PFO) who received different modalities of treatment—systemic thrombolysis (40%), anticoagulation alone (36%), surgical thrombectomy (16%), and percutaneous thrombectomy (8%). Patients receiving systemic thrombolysis and surgical thrombectomy had more favorable outcomes in terms of survival to discharge compared to patients who received anticoagulants alone [79••].

Several prospective and retrospective studies have linked the presence of PFO with increased prevalence of ischemic stroke (clinical or silent) in the patients with acute VTE [82•, 84–86]. Under the physiological conditions, the flap-like PFO defect is passively closed due to left to right pressure gradient. However, this gradient may be reversed during acute PE which results in RLS [87]. In patients with high-risk PE, acute rise in pulmonary hypertension and resultant right heart strain leads to profound and persistent RLS providing a passage for venous thrombi to travel across PFO. In a large prospective study, Le Moigne and colleagues quantified the prevalence of subsequent stroke in 361 consecutive patients presenting with symptomatic PE with and without PFO [72]. The study concluded that presence of PFO was an independent risk factor due to a fourfold increased risk of ischemic stroke. Of note, authors also noticed higher risk of stroke when ASA was present. It is postulated that septal excursions due to ASA allows more flow through PFO leading to increased risk of thrombi migration [88, 89]. Due to such a high risk of stroke, systematic screening of PFO is essential in this population [90••]. Although TEE

is considered a gold standard test to diagnose PFO [91], according to 2016 American society of echocardiography guidelines [91], screening with either TTE or TEE with agitated saline contrast has comparable accuracy [92, 93]. However, in either scenario—repeated provocative Valsalva maneuver is crucial to improve accuracy of detecting PFO [94].

Among patients with PE and/or DVT and confirmed PFO, there should be higher suspicion and scrutiny for silent ischemic events, mainly with diffusion-weighted brain MRI [95•]. Clergeau et. al [86] studied 60 consecutive patients admitted with PE. All patients underwent clinical neurological assessment followed by diffusion-weighted brain MRI and contrast TTE on the day after admission. PFO was diagnosed in 15/60 (25%) patients. The frequency of silent brain infarcts was significantly higher in patients with PFO compared to non-PFO (5/15 versus 1/45, $p=0.003$) group. At times, the patterns of ischemic brain lesions on diffusion-weighted MRI helped to distinguish between PFO-stroke compared to other etiology of embolic stroke. In a retrospective qualitative comparison study of 117 PFO-stroke patients to 358 patients with atrial fibrillation-stroke (AF-stroke), Kim and colleagues [96] showed that a PFO-stroke usually appears as a single cortical or multiple small (<15 mm) scattered ischemic lesions in the vertebrobasilar circulation without any visible vessel occlusion on angiography.

Cryptogenic stroke (CS) is thought to comprise of ~25% of all acute ischemic strokes [97]. Although a prospective study showed that PFO is not an independent risk factor for future cerebrovascular events in general population [98], various studies have demonstrated a higher prevalence of PFO in CS in all age groups despite adjudicating for known risk factors for stroke [99–101]. Ozdemir et al. described that significant history of VTE, migraine, recent prolonged travel, sleep apnea, or a Valsalva maneuver preceding the event are established clinical clues indicating paradoxical embolism among patients with CS [102]. As such, a low threshold should exist to look for VTE in patients with CS linked to PFO when suspicion is high [95•]. However, the absence of DVT on lower extremity ultrasound after CS does not necessarily rule out venous origin of source of embolism as a small clot might have dislodged or dissolved [103]. Mounting evidence suggests that PFO device closure is more effective than medical therapy alone for secondary prevention of suspected embolic stroke of uncertain etiology (ESUS) in select patients aged less than 60 years with large PFO with or without associated ASA [104–106]. According to a 2018 meta-analysis of 4 high-quality RCTs enrolling 2531 patients [107•], PFO closure led to 60% reduction in recurrent ischemic strokes over 3–6 years follow-up period.

Miscellaneous Conditions and Risk of Stroke

May-Thurner Syndrome and Risk of Stroke

May-Thurner syndrome (MTS) (also known as iliac vein compression syndrome or Cockett's syndrome) is a rare anatomical variant where right iliac artery compresses left iliac vein against the lumbar spine leading to increased risk of left leg DVT [108, 109•]. In a retrospective study of 470 CS patients undergoing PFO closure at a single center, Kieran et al. found 30/470 (6.3%) patients had MTS on MR venography of pelvis. While majority of them were women (80%), 40% had thrombophilia and 54% women were taking birth-control pills [110]. In another retrospective study of 214 patients with CS comparing 50 controls, not only prevalence of MTS and PFO was significant higher in CS patients ($p=0.0001$, $p=0.0023$, respectively), but compression of left iliac vein was also significantly greater (32% vs 13%, $p<0.00001$) [111].

COVID-19 Infection and Risk of VTE and Stroke

Severe acute respiratory syndrome coronavirus (SARs-CoV-2) has resulted in a global pandemic of COVID-19, with more than 130 million cases and 2.8 million deaths by the end of March 2021 [112]. Although predominantly known as a respiratory illness, its inflammatory response predisposes to thrombotic complications such as MI, VTE, and ischemic stroke [113]. The risk of VTE in patients with COVID-19 admitted to the ICU has been estimated between 20 and 40% [114]. Additionally, a systematic review of 55,176 COVID-19 patients reported an average incidence of stroke as 1.74% (95% CI: 1.09–2.51%), with an average stroke mortality of 31.76% (95% CI: 17.77–47.31%) [115•]. Proposed mechanisms for ischemic strokes in this population includes systemic inflammatory response, comorbid cardiovascular conditions, as well as direct invasion of the brain parenchyma by SARS-CoV-2 [115•, 116].

VTE and Risk of Malignancies

Cancer is a known risk factor for VTE with a sevenfold increase incidence of VTE associated with malignancy [117]. The underlying mechanism for this involves a complex array of molecular interactions driven by the expression of hemostatic proteins, adhesion molecules, inflammatory cytokines, proangiogenic factors, microparticles by tumor and host cells, and even vascular compression from tumor burden [118, 119]. Thrombotic sequelae of cancer can also manifest in other ways, including a nearly twofold

increase in ischemic stroke incidence [120], as well as disseminated intravascular coagulation (DIC) and Trousseau syndrome (TS). TS is the manifestation of migratory thrombophlebitis in the setting of malignancy. Though the exact mechanism remains unclear, it is often seen in mucin-producing cancers such as gastric cancer. Embolic stroke diagnosed in malignancy, especially when occurring in disparate cerebral regions, should raise suspicion for TS [121•, 122–124]. Cerebral infarction from TS has been documented across a wide spectrum of malignancies from benign adenomyosis to thyroid cancer [121•, 125].

One-year cumulative incidence of VTE following malignancy is varied after solid tumors—brain (6.9%), pancreas (5.3%), stomach (4.5%), and lung (2.4%)—and hematological malignancies, acute myelogenous leukemia (3.7%) and chronic myelogenous leukemia (1.5%) [120, 126]. Patients with metastases have a higher risk compared to those without (OR 19.8) [117]. Depending on the type of CNS malignancy, annual VTE incidence ranges from 0.5 to 20% [127]. Glioblastoma is the CNS tumor with highest incidence of VTE (15.7%), while meningioma rarely leads to VTE (<1%) [128]. Other tumor-related risk factors leading to increased risk of VTE include larger size, intraluminal thrombosis, IDH1 wild-type, high soluble P selectin levels, and podoplanin expression [129••, 130, 131], as well as subtotal surgical resection, use of corticosteroids, anti-VEGF therapy, leukocytosis, and thrombocytopenia [128, 132, 133]. Notably, patients with malignant gliomas who develop VTE within the first 2 years have a 30% higher risk of death [134].

Atypical Presentations of Pulmonary Embolism

Syncope and Pulmonary Embolism

Syncope is not a classical presentation of PE, but not an uncommon one with an estimated incidence of 13% in all patients with PE [135]. It can be explained by three possible mechanisms [135]. (1) Occlusion of the pulmonary vascular tree causing right ventricular failure and impaired left ventricular filling, leading to a reduction in cardiac output, arterial hypotension, cerebral hypoperfusion, and, ultimately, loss of consciousness. (2) Right ventricular overload and dilatation predisposing to a variety of arrhythmias, including ventricular tachycardia or ventricular fibrillation. In patients with pre-existing conduction system disease, the development of a right bundle branch block commonly seen in acute pulmonary embolism can cause complete AV block and other brady-dysrhythmias.

(3) Finally, PE may trigger a neurogenic syncope via a vasovagal reflex. The Bezold-Jarisch reflex of bradycardia and coronary vasodilation can lead to profound systemic hypotension, cerebral hypoperfusion, and syncope in acute RV ischemia [136, 137].

Among all presentations of PE, syncope portends a worse prognosis [138–145], though some contradictory studies show no difference in mortality [135, 145–147]. In the International Cooperative Pulmonary Embolism Registry, the 3-month mortality rate of patients with syncope was 26.8% compared to 17% in the non-syncope PE population [148]. Syncope was associated with a higher prevalence of hemodynamic instability (OR 3.5), echocardiographic signs of RV dysfunction (OR 2.1), 30-day all-cause mortality (OR 1.73), and PE-related 30-day adverse outcomes (OR 2.0) [149••]. Conversely, in patients with syncope, prevalence of PE is around 8–17% [67, 135, 146, 150–152]. In most studies, syncope led to a diagnosis of acute PE in the setting of other symptoms like chest pain, dyspnea, tachycardia, or tachypnea [153]. Certain factors which have been shown to predict syncope in PE patients are larger clot burden [154, 155], central location of PE [147, 156], and saddle embolism [147].

Seizures and Pulmonary Embolism

PE can present heterogeneously, with seizures being one of the rarest and most interesting clinical manifestations. Mostly described in the literature as case reports [157–160], acute PE presenting with new onset seizures is believed to occur in less than 1% of PE cases [157]. Potential pathophysiology includes hypoxia-driven cardiogenic seizures, with right ventricular failure and decreased cardiac output leading to transient global cerebral hypoperfusion [158]. A literature review by Zuin et al. [161••] identified 16 case reports where focal and generalized seizures were identified in 37.5% and 50% of PE cases, respectively, with the remainder lacking sufficient data for diagnosis. Neurologic comorbidities such as history of childhood epilepsy, stroke, and syncope were identified in 25% of the patients. Eleven of the 16 patients were hemodynamically stable on admission, with systemic thrombolysis eventually being used in 5 cases. The reported mortality rate was 54.5%, with diagnosis of PE retrospectively made at autopsy in 25% of patients. The high mortality rate is largely attributed to delay in diagnosis, a challenge also described in previous case reports [160, 162, 163]. Clinicians have the difficult task of recognizing underlying PE in the presentation of seizure while also ruling out concomitant ICH prior to starting treatment [161••]. Further investigation needs to be aimed at identifying the predisposing risk factors, clinical presentation, and treatment for these challenging cases.

Peripheral Nervous System Complications of VTE

VTE, and the treatment of VTE, can affect the PNS in a number of ways. The most common mechanism of peripheral nerve injury in connection with VTE is a post-thrombotic syndrome (PTS). Up to half of all patients with acute proximal DVT will develop PTS, and 5–10% will develop severe symptoms [164]. The mechanism of neuropathic pain associated with PTS appears to be a combination of both inflammation surrounding affected nerves and possibly a demyelinating process [165]. While the treatment of PTS is centered on symptomatic management of the neuropathic pain, prevention relies on the use of elastic compression stockings to reduce venous hypertension and exercise [164].

In addition to PTS, peripheral neuropathy from VTE can occur, although rarely, due to direct entrapment neuropathy from DVT or due to VTE treatment. Femoral neuropathy can develop as a consequence of VTE through retroperitoneal hematoma from anticoagulation [166]. Moreover, direct damage to the femoral nerve via transfemoral approaches in CDT or mechanical thrombectomy is possible with an incidence of 1.5% [167]. VTE of the crural veins causing entrapment neuropathy has been described in case reports of peroneal neuropathy resulting in foot drop [168, 169]. In the upper extremity, brachial vein DVT has been reported as a cause of cubital tunnel syndrome [170]. Median nerve entrapment neuropathy secondary to spontaneous hemorrhage into the carpal tunnel following anticoagulation for VTE has also been reported [171].

Conclusions

VTE is known to have heterogeneous presentations leading to morbid or fatal outcomes. While cardiovascular complications of DVT/PE are well-known, neurologic consequences of VTE are mainly known for ICH which is indirectly linked to the treatment of VTE. In addition to ICH, this review has described the other potential yet underdiagnosed complications of VTE such as acute ischemic strokes, risk of CS in the setting of right-to-left intracardiac shunts, and some of the peripheral entrapment neuropathies due to DVT and post-thrombotic syndrome. The association between VTE and neurologic complications is complex, and further investigation is needed to guide management.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
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